Serum Testosterone Concentrations and Urinary Bisphenol A, Benzophenone-3, Triclosan, and Paraben Levels in Male and Female Children and Adolescents: NHANES 2011-2012

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ABSTRACT

Background: Exposure to environmental phenols (e.g., bisphenol-A, benzophenone-3, and triclosan) and parabens is widespread in the population. Many of these chemicals have been shown to have anti-androgenic effects both *in vitro* and *in vivo.*

Objective: To examine the association of bisphenol-A (BPA), benzophenone-3 (BP-3), triclosan (TCS), and parabens with serum total testosterone (TT) levels in child and adolescent participants (ages 6-19 years) in the National Health and Nutrition Examination Survey (NHANES) 2011-2012.

Methods: We performed multivariable linear regression to estimate associations between natural log-transformed serum TT and quartiles of urinary BPA, BP-3, TCS, and parabens in male and female children (ages 6 – 11 years) and adolescents (ages 12 - 19 years).

Results: BP-3 and BPA were associated with significantly lower TT in male adolescents, and BPA was associated with significantly higher TT in female adolescents. TT was not consistently associated with TCS or total parabens in children or adolescents of either sex.

Conclusions: To our knowledge, this is the first study to report an association between BP-3 and BPA with serum TT in adolescents. Associations between BPA and TT differed according to sex in adolescents, with inverse associations in boys and positive associations in girls. BP-3 was associated with significantly lower TT in adolescent boys only. However, because of the limitations inherent to the cross-sectional study design, further studies are needed to confirm and elucidate on our findings.

INTRODUCTION

Endocrine disruptors compounds (EDCs) are synthetic and naturally occurring chemicals that may interfere with endogenous endocrine action; particularly, *in utero* exposure or exposure during puberty may produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. Exposure to EDCs has been associated with reproductive problems, obesity, diabetes, cancers, and behavioral and learning disorders (reviewed in WHO 2013). Several substances are thought to cause endocrine disruption; most EDCs are classified as xenoestrogens while others inhibit androgen production and function (Meeker 2012). One class of EDC is the environmental phenols, which includes bisphenol A (BPA), triclosan (TCS), and benzophenone-3 (BP-3). People are exposed to environmental phenols through industrial pollution, food consumption, and the use of personal care and consumer products. Parabens are another class of EDC that are prevalent in the environment. These substances are used in cosmetics, pharmaceuticals, as antimicrobial preservatives against mold, and in food and beverage packaging (Calafat et al. 2010).

Bisphenol-A is considered to have both estrogenic and anti-androgenic effects. In a recent review of the BPA literature, Peretz et al. (2014) concluded that BPA is a reproductive toxicant based on findings from experimental and epidemiological studies, with strong evidence that BPA is an ovarian toxicant in human females and animal models, and limited evidence of effects on other reproductive outcomes in men, women, and animals. In rat models, prenatal or perinatal BPA exposure has been shown to have adverse effects on the male reproductive system including decreased epididymal weight and reduced testicular sperm counts (Salian 2009a, 2009b). Additionally, decreased testosterone (T) levels have been observed in rodents exposed to

BPA during the prepubertal (Takao et al. 1999) and pubertal period (Herath et al. 2004). The available body of literature suggests that BPA is probably a testicular toxicant in animals, but the data in humans is more ambiguous (Peretz et al. 2014).

Triclosan has demonstrated anti-androgenic action in *in vitro* studies. Competitive binding assays with a recombinant androgen receptor (AR) have shown that TCS binds to the receptor with relatively high avidity (Gee et al. 2008). The TCS-AR interaction was also confirmed in T47D human breast cancer cell line (Ahn et al. 2008).

The evidence for reproductive effects following exposure to BP-3 have been less extensively investigated. We identified a single panel study of 15 young men (age 23–29 years) and 17 postmenopausal women (age 54–86 years) that compared average levels of reproductive hormones after topical application of cream containing BP-3 (10% wt/wt) to levels after application of a control cream. Although some differences were observed, the authors concluded they were probably chance findings (Janjua et al. 2004). Evidence for reproductive effects comes largely from *in vitro* studies that have demonstrated both estrogenic and anti-androgenic effects of BP-3 (Reviewed in Kraus et al. 2012). Moreover, some experimental animal studies have looked at BP-3, but these focus mostly on adult animals with few studies looking at early development (Reviewed in Kraus et al. 2012).

In vivo studies of the effect of parabens on testosterone levels have produced mixed results. Rats and mice exposed *in utero* to parabens showed a significant reduction of testosterone levels and mature sperm counts (Kang et al. 2002; Oishi 2002a, 2002b), whereas other studies found no significant changes (Hoberman et al. 2008; Taxvig et al. 2008).

Data from the National Health and Nutrition Examination Survey (NHANES), collected by

the Centers for Disease Control and Prevention (CDC), have shown widespread exposure to

BPA, BP-3, TCS, and parabens among the U.S. general population, including children and

adolescents. The NHANES 2011-2012 cycle includes serum total testosterone (TT)

measurements in participants 6 years of age and older. Because of existing concerns about the

anti-androgenic activity of environmental phenols and parabens, we evaluated the relationship of

TT with urinary levels of BPA, BP-3, TCS, and total parabens (∑PAR) among male and female

children (ages 6-11 years) and adolescents (ages 12-19 years) in a representative U.S. population

sample.

METHOD

Study population

NHANES is a cross-sectional, nationally representative survey of the non-institutionalized

civilian population of the United States conducted annually by the National Center for Health

Statistics (NCHS), CDC (Johnson et al. 2013). For our study, we used the publicly available files

for NHANES cycles 2011-2012. The survey employs a multistage stratified probability sample

based on selected counties, blocks, households, and persons within households.

NCHS-trained professionals conducted interviews in participants' homes; extensive physical

examinations, including blood and urine collection, were conducted at mobile exam centers. All

procedures were approved by the NCHS Research Ethics Review Board (Continuation of

Protocol #2011-17 http://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants provided

written informed consent. In the 2011-2012 data set, urinary concentrations of environmental

phenols and parabens were measured in a randomly selected one-third subsample of persons 6

years of age and older by the CDC's National Center for Environmental Health (NCEH),

Division of Laboratory Sciences (DLS), which coordinates the National Biomonitoring Program

(NBP) to assess nutritional status and exposure of the U.S. population to environmental

chemicals and toxic substances. For our analysis, we included only those participants who had

measurements for urinary phenols and parabens and information regarding the covariates

included in the model (n=588).

Serum Total Testosterone

Serum samples were shipped to the CDC/NCEH/DLS where the serum total testosterone

(TT) was analyzed by isotope dilution liquid chromatography tandem mass spectrometry.

Information regarding reliability, validation and quality control for serum total testosterone are

described in the NHANES laboratory method

(http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/TST_G_met.pdf). Serum TT was natural

log-transformed for analyses because the distribution of this variable was skewed left.

Urinary biomarkers

Spot urine samples were collected from study participants and stored at −20°C; they were

then analyzed by NCEH/DLS. BPA, BP-3, TCS, methyl paraben (MPB), and propyl paraben

(PPB) were measured by solid phase extraction coupled on-line to high performance liquid

chromatography and tandem mass spectrometry. Details of detection and measurement of the

urinary compounds are described in the NHANES laboratory method

(http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/lab_methods_11_12.htm). The reported

results for all assays meet the NCEH/DLS quality control and quality assurance performance

criteria for accuracy and precision (NCHS 2013). The limits of detection (LOD) were 0.4ng/mL

for BPA, 0.4ng/mL for BP-3, 2.3 ng/mL for TCS, 1.0 ng/mL for MPB, and 0.2ng/mL for PPB.

Urinary concentrations of the compounds below the level of detection were assigned the limit of

detection divided by the square root of 2, as recommended by NHANES (NCHS 2013). To

account for variation in dilution in spot urinary samples, we adjusted for urinary creatinine by

including it as a model covariate (Barr et al. 2005; Ikeda et al. 2003). The parabens ($\sum$PAR) were

considered together as a sum of total parabens (MPB and PPB), calculated by adding the

concentration of each individual metabolite (Buttke et al. 2012). There were no significant

correlations between the urinary compounds (data not shown), except between urinary $\sum$PAR

and TCS or BPA as indicated by the Pearson correlation coefficients (r = 0.18, p<0.0001; and r =

0.08 p<0.04, respectively).

Covariates

All models were adjusted for the following *a priori* covariates: age, race/ethnicity, urinary

creatinine, poverty income ratio (PIR), obesity, season of collection, time of venipuncture, total

serum cholesterol, serum cotinine as a biomarker of exposure to environmental tobacco smoke,

and physical activity (only for male and female adolescents). Race/ethnicity was categorized as

non-Hispanic white, non-Hispanic black, Hispanic (Mexican-American and other Hispanic), and

other. PIR is a measure of socioeconomic status and represents the calculated ratio of household

income to the poverty threshold after accounting for inflation and family size; it was entered as a

continuous variable. Time of venipuncture is found in the NHANES Fasting Questionnaire File

and was classified as morning, afternoon, or evening sessions. Season of collection was obtained

from the NHANES demographic data pertaining to the six month time period when the examination occurred; this was from either November 1st – April 30th or May 1st – October 31st. We included this covariate due to the differences in usage of these products (i.e. use of sunscreen with BP-3 and parabens increase during the summer). Moreover, levels of TT in men have a wide range of variation due to diurnal, weekly and, also, seasonal variations (Brambilla et al. 2009; Cunningham and Toma 2011). Children and adolescents were classified as underweight, normal weight, overweight, or obese according to age and sex, as defined by NHANES (Body Measures File). For our analyses, we combined underweight and normal weight as one category. Serum cotinine and urinary creatinine were natural log-transformed. Information on recreational physical activity was available for adolescents only; participants were asked whether they engaged in regular moderate and/or vigorous recreational activities (categorized as yes or no).

In addition to models adjusted for the covariates indicated above, we ran a second model for each exposure that was adjusted for urinary concentrations of the other three exposures, which were modeled as natural log-transformed continuous variables.

Statistical Methods

All analyses were performed using the weight from the urinary phenols and parabens subsample, as recommended by NCHS, to account for the complex sampling design and non-response of NHANES; all analyses were performed according to NHANES guidelines (Johnson et al. 2013). SAS 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses, and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the NHANES complex sample design. P-values were presented at the significance level < 0.05.

Analyses were conducted for male children (6-11 years), male adolescents (12-19 years), female children (6-11 years), and female adolescents (12-19 years). We used multivariable linear regression to calculate adjusted β-coefficients for the associations between natural log-transformed TT and urinary phenol and paraben levels among the participants. Urinary BPA, BP-3, TCS, and ∑PAR were categorized according to quartiles defined for each population subgroup.

Since our dependent variable, TT, was log-transformed, the results were re-transformed by exponentiation of the β coefficients and presented as percent differences estimated by comparing each of the upper 3 quartiles to the lowest quartile. Statistical tests for linear trends were conducted by modeling quartiles as an ordinal variable using integer values.

RESULTS

Table 1 presents the characteristics of the study population by age and sex. The geometric mean (GM) serum TT levels for male children, male adolescents, female children, and female adolescents were 3.75 ng/dL, 276.07 ng/dL, 5.80 ng/dL, and 22.78 ng/dL, respectively (Table 1). There was a statistically significant difference in mean urinary TCS and ∑PAR levels between female children and female adolescents ($p < 0.05$) (data not shown). There were no other statistically significant differences in urinary compound levels between age- and sex-specific groups (i.e., differences in mean urinary levels between male children and adolescents, differences in mean urinary levels between male and female adolescents, etc.).

Benzophenone-3 (Table 2): Male adolescents in the 3rd and 4th quartiles of BP-3 had significantly lower TT (-38.74%; 95% CI: -58.52%, -10.42%; and -36.87%; 95% CI: -59.34%, -1.98%, respectively, based on Model 1) than males in the lowest quartile. Although the association was strongest for the 3rd quartile, the overall trend was significant (*P*-trend = 0.01). This pattern of associations persisted following adjustment for BPA, TCS, and ∑PAR (Model 2). In female adolescents, TT was significantly higher for girls in the second versus first quartile of BP-3 exposure, but positive associations were closer to the null and non-significant for the third and fourth quartiles of exposure (*P*-trend 0.14). Associations were similar after adjustment for BPA, TCS, and ∑PAR, but no longer significant for quartile 2. There were no significant associations between TT and BP-3 in male or female children, and no evidence of consistent trends with increasing quartiles of exposure.

Bisphenol-A (Table 3): Mean TT was lower for all quartiles of exposure above the reference level in male adolescents (*P*-trend = 0.01), with significant associations for the 2rd and 4th quartiles of BPA (-49.34%; 95% CI: -70.18%, -13.06%; and -53.70%; 95% CI: -70.77%, -26.66% respectively, Model 1). By contrast, TT was positively associated with BPA exposure in female adolescents, with a monotonic increase in mean TT with increasing quartiles of exposure (*P*-trend = 0.01) and significantly higher TT for the 4th quartile (53.73%; 95% CI: 9.42%, 113.83%) compared with the lowest quartile. BPA did not appear to be associated with TT in male or female children. Estimated associations and overall patterns were similar for all population subgroups after adjustment for BP-3, TCS, and ∑PAR.

Triclosan (Table 4): Mean TT was lower for all quartiles of TCS compared with the lowest quartile in all population subgroups, and trend *P*-values were significant for male children and

adolescents (*P*-trend = 0.02 and 0.04, respectively.) However, Model 1 quartile-specific

decreases were significant only for the third quartile in male adolescents and in female children,

and mean values were closest to the null for the highest quartile in male children and adolescents

and in female children, while all associations were close to the null for female adolescents.

Associations were generally consistent with Model 1 estimates after adjustment for BP-3, BPA,

and ∑PAR, though the negative association with quartile 3 was only significant in female

children, and the *P*-trend was significant only for male children.

Parabens (Table 5): There were no statistically significant associations between TT and ∑PAR

in any subgroup before or after adjustment for BP-3, BPA, and TCS, and no evidence of

consistent trends with increasing quartiles of exposure.

DISCUSSION

To our knowledge, this is the first study to investigate the associations between BPA, BP-3,

TCS, and ∑PAR with serum TT in children and adolescents. In this cross-sectional analysis of

data from NHANES 2011-2012, both urinary BPA and urinary BP-3 levels were inversely

associated with serum TT in male adolescents; conversely, higher levels of BPA were associated

with higher serum TT in female adolescents. No significant associations were observed in

children (male or female). Overall, there was little evidence of associations between TCS and

TT, and no significant associations with ∑PAR in any of the four population subgroups.

Associations between BPA levels and TT differed between male and female adolescents, with an

inverse association in males and a positive association in females. As reviewed by Gore et al. (2015),

several animal studies have focused solely on the associations of BPA with serum testosterone in

male animals; these studies have consistently reported decreased serum testosterone levels in these

animals. However, other studies have looked at both male and female animals, and several of these

studies have reported sex differences in testosterone levels following BPA exposure. Chen et al.

(2014a) reported significantly lower serum testosterone in male rats exposed to BPA compared to

controls, whereas BPA-exposed female rats had non-significantly higher serum testosterone.

Fernandez et al. (2010) reported increased serum testosterone and serum estradiol levels in female

rats exposed postnatally to BPA. Furthermore, Xi et al. (2011) reported that the expression of several

genes related to the hypothalamic-pituitary-gonadal (HPG)-axis was increased in both male and

female mice pups following BPA exposure; several hormonal changes including decreased

testosterone synthesis in male pups and enhanced aromatase expression levels and estrogen synthesis

in female pups were contemporarily observed, suggesting that the changes in gene expression may

have affected downstream hormonal levels.

Levels of serum TT in men have a wide range of variation due to diurnal, weekly, and

seasonal variations, episodic secretion, and glucose ingestion (Brambilla et al. 2009;

Cunningham and Toma 2011). Diurnal variation results in peak serum TT levels in the early

morning followed by a progressive decline to the lowest levels in the evening, which may be as

little as 15% lower than peak morning levels, and as much as 50% lower in younger males

(Paduch et al. 2014). Testosterone circulates in the body either bound to sex-hormone binding

globulin (SHBG), albumin, or corticosteroid binding globulin (CBG), or in an unbound form

(free). SHBG-bound T represents approximately 44% of TT and is tightly bound and unavailable

to cells. Albumin-bound T and CBG-bound T represent approximately 50% and 4% of TT, and

for both, T is weakly bound and dissociates rapidly. Free testosterone (FT) represent about 2-3%

of TT (De Ronde et al. 2006). The term "bioavailable" T refers to the sum of the CBG-bound,

albumin-bound, and free components, thus representing the T fraction available to cells. In the

present study, we evaluated total testosterone, which includes both bioavailable and bound forms.

Few epidemiological studies have examined relationships between BPA and sex hormones,

and study populations have been limited to adults. Our finding of a positive association of BPA

and TT in female adolescents are in agreement with the findings reported by Takeuchi and

Tsutsumi (2002) and Takeuchi et al. (2004). Takeuchi and Tsutsumi (2002) investigated the

relationship between BPA exposure and hormone levels in men (n = 11) and women (n = 30),

showing positive correlations between serum BPA concentrations with TT and FT levels in both

sexes. A significant, positive relationship was reported between circulating androgen

concentrations and BPA exposure in a small study of 26 normal women and 47 women with

ovarian dysfunction (Takeuchi et al. 2004). The inverse association of BPA and serum TT that

we found in male adolescent may be consistent with epidemiological studies conducted in male

adults (Meeker et al. 2010; Mendiola et al. 2010; Zhou et al. 2013) Recently, Zhou et al. (2013),

in a cross-sectional study of 290 men with or without BPA exposure in the workplace, found that

serum BPA was significantly associated with decreased FT levels, decreased FAI, and increased

SHBG levels. Mendiola et al. (2010) examined urinary BPA and serum hormones in fertile men

(n=360) and found a significant inverse association between urinary BPA concentration and free

androgen index (FAI) concentration levels as well as a significant positive association between

BPA and SHBG levels. In a subset of 167 men attending an infertility clinic, Meeker et al.

(2010) found that in 167 men recruited through an infertility clinic, urinary BPA concentrations

were inversely associated with serum inhibin B, FAI and estradiol /testosterone index (a marker

of aromatase activity). Additionally, they found a positive association between urinary BPA

with both FSH and FSH/inhibin B ratio (a marker of Sertoli cell function). Conversely, several

studies reported a positive association of BPA and testosterone in male adults (Galloway et al.

2010; Hanaoka et al. 2002; Takeuchi and Tsutsumi 2002). Hanaoka et al. (2002) reported that

urinary concentrations of BPA were significantly higher in 42 exposed workers than in matched-

controls (n=42) and that urinary BPA level was inversely correlated with serum follicular-

stimulating hormone (FSH) concentrations (Hanaoka et al. 2002). Galloway et al. (2010) found

that higher daily BPA excretion was associated with a higher TT concentration in 307 men from

the InCHIANTI study among adults male in Italy.

To our knowledge, the only epidemiological study investigating the association of urinary

BP-3 with sex hormones was conducted by Janjua and colleagues (2004). The authors reported

that the mean serum testosterone concentration in 15 young men was significantly lower 4 hours

after they were treated with cream containing BP-3 compared with levels 4 hours after a control

cream was applied. However, there was no significant difference 24 hours after application of the

BP-3 or control cream. Testosterone levels were also lower in 17 postmenopausal women after

application of the BP-3 versus control cream, but because testosterone levels were lower before

and after the BP-3 cream was applied, the authors attributed the finding to chance.

The present study has several important limitations. First, the cross-sectional nature of this

study limits the inferences that can be made based on the results. Moreover, 12–19-year old boys

and girls classified as adolescents may have included a mix of children who were pre- and post-

pubescent. Recently, Lopez-Espinosa and colleagues (2011), in their study of the association

between sex hormones and perfluorocarbon compounds, considered total testosterone > 50

ng/dL, to be a cutoff for reaching puberty in male children/adolescents. Based on this cutoff, we

found that at age 10 and at age 11, 7.59% and 29.17% of male participants had reached puberty,

respectively; no male children under the age of 10 had reached puberty based on this cutoff

point. On the other hand, for those 12 years and 13 years of age, 67.16% and 83.56% had

reached puberty, respectively; all male adolescents over the age of 13 had total serum

testosterone levels higher than 50 ng/dL (data not shown). Therefore, the age cutoff used in this

study to classify boys as children or adolescents seems appropriate.

Recent findings from experimental studies suggest that BPA may affect aromatase activity,

which might subsequently lead to changes in concentrations of FT, FAI, or estradiol (E2), and in

the E2/T ratio. For example, Castro et al. (2013) reported increased aromatase activity in adult

male Wistar rats exposed to BPA, concurrent with decreased testosterone and increased E2 and

E2/T ratio levels. E2 and aromatase activity increased in the urogenital sinus of fetal mice after

maternal exposure to low-dose BPA (Arase et al. 2011). Furthermore, BPA-induced aromatase

activation was reported by Kim et al. (2010) in rat testicular Leydig cells and by Nativelle-

Serpentini et al. (2003) in human placenta JEG-3 cells following pre-incubation times ranging

from 10 minutes to 6 hours, whereas Chen et al (2014b) showed that BPA did not induce

aromatase activation in human MCF-7 breast cancer cell lines, instead functioning as an estrogen

receptor agonist. Conversely, other *in vitro* studies have reported aromatase inhibition by BPA

(Benachour et al. 2007; Bonefeld-Jørgensen et al. 2007). These hormones were not measured for

the 2011–2012 NHANES survey, so we were unable to investigate if there was any association

with BPA in the population of interest.

The use of a single spot measurement of serum testosterone is also a limitation given cyclical

variation in hormone levels. We adjusted for the time of day (session) when the sample was

collected (morning, afternoon, or evening) and for the season of collection (November 1 – April

30 or May 1 – October 31), but residual confounding is possible if the timing or season of

sample collection was associated with exposure levels. Another important limitation is the use of

single spot urinary phenols and parabens measurements. Because these chemicals are short lived

in the body, a biomarker of longer-term exposure would have been better. It has been shown that

a single sample of BPA may be predictive of long-term exposure; Mahalingaiah et al. (2008)

reported that study participants were correctly classified as being in the highest tertile of BPA

exposure about two-thirds of the time, based on data from 31 men and women attending an

infertility clinic. However, overall, the use of the single spot measurements of exposure is a

limitation of this study. There may also have been other confounding factors that we did not

control for in our analyses, including exposure to other environmental chemicals that are

potentially anti-androgenic, such as phthalates (Meeker and Ferguson 2014).

CONCLUSION

In conclusion, urinary levels of BP-3 and BPA were associated with lower levels of

serum testosterone in male adolescents (age 12–19 years), while BPA was positively associated

with serum total testosterone in female adolescents in NHANES 2011-2012. These findings are

of interest due to the pervasiveness of these chemicals in our environment and the potential

impact that altered reproductive hormones, such as testosterone, can have on the development

and overall health of children and adolescents. Because of the limitations of this study, our

results should be interpreted with caution. However, our results support the need for future

studies to confirm our findings and investigate potential mechanisms for differences between

males and females, including longitudinal observational studies of associations between long-

term exposures to EDCs and endocrine and reproductive hormone levels, and experimental

animal and in vitro studies of the effects of low-dose environmentally relevant exposures.

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Table 1: Weighted Characteristics for children and adolescent (aged 6-19) participants in NHANES 2011-2012.

Characteristic	Male Children	Male Adolescent	Female Children	Female Adolescent
n	134	161	142	157
Urinary Bisphenol-A (BPA) (ng/mL), GM (SE)	1.74 (0.26)	1.94 (0.29)	1.40 (0.17)	1.49 (0.21)
Urinary Benzophenone-3 (BP-3) (ng/mL), GM (SE)	15.57 (4.61)	20.03 (5.69)	18.31 (3.96)	35.59 (14.40)
Urinary Triclosan (TCS) (ng/mL), GM (SE)	8.79 (1.80)	8.55 (1.67)	6.30 (0.72)	12.27 (3.05)
Urinary Total Parabens ($\sum$PAR) (ng/mL), GM (SE)	15.07 (4.19)	18.51 (4.15)	29.51 (6.58)	63.75 (17.23)
Age (Years), GM(SE)	8.39 (0.20)	15.50 (0.19)	8.76 (0.15)	15.20 (0.17)
Serum Total Testosterone (ng/dL), GM (SE)	3.75 (0.60)	276.07 (27.71)	5.80 (0.54)	22.78 (0.73)
Serum Cotinine (ng/mL), GM (SE)	0.06 (0.01)	0.12 (0.02)	0.05 (0.01)	0.14 (0.05)
Urinary Creatinine (mg/dL), GM (SE)	71.18 (6.16)	112.65 (10.23)	68.09 (5.42)	98.87 (11.42)
Total Cholesterol (mg/dL), GM (SE)	15625 (2.27).	148.93 (2.61)	156.42 (3.33)	159.16 (5.82)
Ratio family income to poverty (PIR), GM (SE)	1.65 (0.09)	1.73 (0.25)	1.76 (0.18)	1.73 (0.22)
Obesity[a]				
Normal/Underweight, % (SE)	93.83 (1.93)	59.12 (3.11)	86.16 (3.16)	64.21 (8.17)
Overweight, % (SE)	5.14 (2.31)	23.40 (3.64)	9.07 (3.85)	16.25 (4.16)
Obese, % (SE)	1.03 (0.77)	17.49 (4.58)	4.78 (1.85)	19.54 (6.14)
Race/Ethnicity				
White (Non-Hispanic) % (SE)	54.45 (5.59)	55.06 (4.75)	55.13 (7.84)	55.46 (6.60)
Non-Hispanic Black % (SE)	15.40 (1.97)	15.73 (4.07)	12.21 (3.17)	15.44 (5.05)
Hispanic % (SE)	21.78 (5.12)	22.21 (3.98)	25.10 (5.25)	21.69 (4.07)
Other % (SE)	7.37 (2.49)	7.00 (2.45)	7.57 (2.12)	7.41 (1.44)
Session time of venipuncture				
Morning	42.20 (5.42)	51.94 (6.77)	53.74 (4.01)	42.36 (4.89)

Afternoon	31.88 (3.96)	29.45 (4.98)	30.16 (4.51)	36.83 (4.64)
Evening	25.92 (4.75)	18.61 (5.37)	16.10 (3.06)	20.81 (5.11)
Six month time period when the examination was performed				
November 1 through April 30, % (SE)	52.60 (7.30)	47.64 (9.29)	48.08 (6.93)	40.15 (7.91)
May 1 through October 31, % (SE)	47.40 (7.30)	52.36 (9.29)	51.92 (6.93)	59.85 (7.91)
Physical Activity[b]				
Yes, % (SE)		90.23 (3.05)		71.43 (4.21)
No, % (SE)		9.77 (3.05)		28.57 (4.21)

[a]Children and adolescents were classified as underweight, normal weight, overweight, or obese according to age and sex, as defined by NHANES (Body Measures File).

[b]Information on recreational physical activity was available for adolescents only; participants were asked whether they engaged in regular moderate and/or vigorous recreational activities (categorized as yes or no).

Table 2. Percent differences (95% CI) in serum total testosterone by quartiles of BP-3 exposure, National Health and Nutrition Examination Survey, 2011–2012

BP-3 Exposure	Model 1[a]	Model 2[b]
Male children		
Q1: ≤ 3.5 ng/mL	Ref.	Ref.
Q2: 3.6–8.8 ng/mL	-1.98, (-51.81, 97.39)	7.25, (-46.74, 115.98)
Q3: 8.9–71.1 ng/mL	27.12, (-20.55, 105.44)	31.00, (-25.17, 129.33)
Q4: > 71.7 ng/mL	-1.98, (-44.57, 73.33)	4.08, (-40.55, 82.21)
P-trend[c]	0.53	0.70
Male Adolescents		
Q1: ≤ 4.0 ng/mL	Ref.	Ref.
Q2: 4.1–15.9 ng/mL	-7.69 (-43.45, 50.68)	1.01 (-34.30, 55.27)
Q3: 16.0–48.7 ng/mL	-38.74 (-58.52, -10.42)	-32.97 (-54.16, -1.98)
Q4: >48.7 ng/mL	-36.87 (-59.34, -1.98)	-32.97(-54.16, -0.50)
P-trend[c]	0.01	0.04
Female children		
Q1: ≤6.6 ng/mL	Ref.	Ref.
Q2: 6.7–13.9 ng/mL	10.52 (-19.75, 50.68)	7.25 (-31.61, 68.20)
Q3: 14.0–58.5 ng/mL	5.13 (-20.55, 39.10)	-0.50 (-50.84, 101.38)
Q4: >58.6 ng/mL	20.92 (-28.82, 105.44)	10.52 (-68.65, 293.54)
P-trend[c]	0.87	0.91
Female adolescents		
Q1: ≤8.6 ng/mL	Ref.	Ref.
Q2: 8.7–23.7 ng/mL	20.92 (3.05, 43.33)	17.35 (-1.00, 39.10)
Q3: 23.8–164.0 ng/mL	10.52 (-18.13, 49.18)	12.75 (-16.47, 50.68)
Q4: >164.0 ng/mL	11.63 (-23.66, 64.87)	16.18 (-21.34, 71.60)
P-trend[c]	0.14	0.27

[a]Adjusted for age, race/ethnicity, serum cotinine, urinary creatinine, total cholesterol, income, obesity, season of collection, time of venipuncture, and physical activity (for adolescents only).

[b]Adjusted for Model 1 covariates plus natural log-transformed BPA, TCS, and ∑PAR.

[c]*P*-value for exposure quartiles modeled as an ordinal variable using integer values.

Table 3. Percent differences (95% CI) in serum total testosterone by quartiles of BPA exposure, National Health and Nutrition Examination Survey, 2011–2012

BPA Exposure	Model 1[a]	Model 2[b]
Male children		
Q1: ≤0.8 ng/mL	Ref.	Ref.
Q2: 0.9–1.5 ng/mL	16.18 (-44.01, 141.09)	9.42 (-46.74, 124.79)
Q3: 1.6–3.3 ng/mL	-14.79 (-62.84, 95.42)	-18.94 (-66.38, 93.48)
Q4: >3.3 ng/mL	-10.42 (-41.14, 37.71)	-22.12 (-55.07, 34.99)
P-trend[c]	0.27	0.19
Male Adolescents		
Q1: ≤0.9 ng/mL	Ref.	Ref.
Q2: 1.0–2.0 ng/mL	-49.34 (-70.18, -13.06)	-50.84 (-71.92, -13.93)
Q3: 2.1–3.7 ng/mL	-36.87 (-62.47, 6.18)	-38.12 (-63.21, 4.08)
Q4: >3.7 ng/mL	-53.70 (-70.77, -26.66)	-52.29 (-71.35, -20.55)
P-trend[c]	0.01	0.02
Female children		
Q1: ≤0.7 ng/mL	Ref.	Ref.
Q2: 0.8–1.4 ng/mL	8.33 (-28.82, 64.87)	18.53 (-36.24, 118.15)
Q3: 1.5–2.8 ng/mL	8.33 (-30.93, 69.89)	19.72 (-42.88, 153.45)
Q4: >2.8 ng/ mL	20.92 (-35.60, 127.05)	40.49 (-56.83, 352.67)
P-trend[c]	0.86	0.94
Female adolescents		
Q1: ≤0.7 ng/mL	Ref.	Ref.
Q2: 0.8–1.5 ng/mL	24.61 (-7.69, 69.89)	27.21 (-4.88, 71.60)
Q3: 1.6–3.2 ng/mL	39.10 (-4.88, 103.40)	36.34 (-6.76, 101.38)
Q4: >3.2 ng/mL	53.73 (9.42, 113.83)	53.73 (12.75, 109.59)
P-trend[c]	0.01	<0.01

[a]Adjusted for age, race/ethnicity, serum cotinine, urinary creatinine, total cholesterol, income, obesity, season of collection, time of venipuncture, and physical activity (for adolescents only).

[b]Adjusted for Model 1 covariates plus natural log-transformed BP-3, TCS, and ∑PAR.

[c]*P*-value for exposure quartiles modeled as an ordinal variable using integer values.

Table 4. Percent differences (95% CI) in serum total testosterone by quartiles of TCS exposure, National Health and Nutrition Examination Survey, 2011–2012

TCS Exposure	Model 1[a]	Model 2[b]
Male children		
Q1: ≤2.5 ng/mL	Ref.	Ref.
Q2: 2.6–6.1 ng/mL	-34.95 (-72.47, 53.73)	-37.50 (-72.75, 41.91)
Q3: 6.2–18.1 ng/mL	-15.63 (-63.58, 93.48)	-17.30 (-62.09, 80.40)
Q4: > 8.1 ng/mL	-10.42 (-52.29, 158.57)	-16.18 (-51.32, 177.32)
P-trend[c]	0.02	0.01
Male Adolescents		
Q1: ≤2.6 ng/mL	Ref.	Ref.
Q2: 2.7–5.7 ng/mL	-32.97 (-63.94, 23.37)	-24.42 (-55.51, 28.40)
Q3: 5.8–19.0 ng/mL	-39.95 (-61.71, -5.82)	-36.87 (-60.94, 2.02)
Q4: >19.0 ng/mL	-10.42 (-41.73, 39.10)	-9.52 (-39.35, 33.64)
P-trend[c]	0.04	0.08
Female children		
Q1: ≤2.3 ng/mL	Ref.	Ref.
Q2: 2.4–3.9 ng/mL	-11.31 (-28.82, 11.63)	22.14 (-34.30, 2.02)
Q3: 4.0–15.3 ng/mL	-32.97 (-52.29, -4.88)	-35.60 (-58.10, -1.00)
Q4: >15.3 ng/ mL	-9.52 (-36.87, 28.40)	-17.30 (-56.83, 60.00)
P-trend[c]	0.11	0.06
Female adolescents		
Q1: ≤2.5 ng/mL	Ref.	Ref.
Q2: 2.6–7.3 ng/mL	-2.96 (-24.42, 24.61)	-3.92 (-27.39, 25.86)
Q3: 7.4–31.6 ng/mL	-4.88 (-30.93, 32.31)	-12.19 (-37.50, 24.61)
Q4: >31.6 ng/mL	-11.31 (-34.30, 20.92)	-10.42 (-34.30, 22.14)
P-trend[c]	0.69	0.88

[a]Adjusted for age, race/ethnicity, serum cotinine, urinary creatinine, total cholesterol, income, obesity, season of collection, time of venipuncture, and physical activity (for adolescents only).

[b]Adjusted for Model 1 covariates plus natural log-transformed BP-3, BPA, and ∑PAR.

[c]*P*-value for exposure quartiles modeled as an ordinal variable using integer values.

Table 5. Percent differences (95% CI) in serum total testosterone by quartiles of ∑PAR exposure, National Health and Nutrition Examination Survey, 2011–2012

∑PAR Exposure	Model 1[a]	Model 2[b]
Male children		
Q1: ≤4.4 ng/mL	Ref.	Ref.
Q2: 4.5–10.1 ng/mL	44.77 (-21.34, 169.12)	43.33 (-17.30, 148.43)
Q3: 10.2–40.0 ng/mL	-15.63 (-46.74, 32.31)	-14.79 (-42.88, 28.40)
Q4: >40.0 ng/mL	10.52 (-37.50, 95.42)	16.18 (-36.24, 113.83)
P-trend[c]	0.22	0.29
Male Adolescents		
Q1: ≤4.9 ng/mL	Ref.	Ref.
Q2: 5.0–10.2 ng/mL	-22.12 (-55.96, 39.10)	-13.06 (-51.36, 53.73)
Q3: 10.3–61.5 ng/mL	-16.47 (-45.66, 27.12)	-3.92 (-32.29, 36.34)
Q4: >61.5 ng/mL	-23.66 (-51.32, 18.53)	-14.79 (-48.31, 41.91)
P-trend[c]	0.49	0.82
Female children		
Q1: ≤11.3 ng/mL	Ref.	Ref.
Q2: 11.4–22.7 ng/mL	13.88 (-12.19, 47.70)	19.72 (-12.19, 63.23)
Q3: 22.8–76.8 ng/mL	12.55 (-21.34, 50.68)	18.53 (-13.06, 63.23)
Q4: >76.8 ng/ mL	31.00 (-4.88, 82.21)	53.73 (-18.13, 191.54)
P-trend[c]	0.39	0.11
Female adolescents		
Q1: ≤15.5 ng/mL	Ref.	Ref.
Q2: 15.6–66.6 ng/mL	-8.61 (-34.95, 29.69)	-5.82 (-32.29, 31.00)
Q3: 66.7–297.9 ng/mL	-21.34 (-43.45, 8.33)	-24.42 (-44.57, 3.05)
Q4: > 297.9 ng/mL	3.05 (-29.53, 52.20)	4.08 (-25.92, 47.70)
P-trend[c]	0.11	0.02

[a]Adjusted for age, race/ethnicity, serum cotinine, urinary creatinine, total cholesterol, income, obesity, season of collection, time of venipuncture, and physical activity (for adolescents only).

[b]Adjusted for Model 1 covariates plus natural log-transformed BP-3, BPA, and TCS.

[c]*P*-value for exposure quartiles modeled as an ordinal variable using integer values.